The Expanding Role of Somatostatin Analogs in the Management of Neuroendocrine Tumors

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ABSTRACT

BACKGROUND: Neuroendocrine tumors (NETs) are neoplasms arising most often in the GI tract, pancreas, or lung. Diagnosis of NETs is often delayed until the disease is advanced, because of the variable and nonspecific nature of the initial symptoms. Surgical resection for cure is therefore not an option for most patients.

METHODS: Somatostatin analogues represent the cornerstone of therapy for patients with NETs. This article reviews the important role that somatostatin analogues continue to play in the treatment of patients with NETs.

RESULTS: Octreotide was the first somatostatin analogue to be developed; more than 30 years of data have accumulated demonstrating its efficacy and safety. Lanreotide is another somatostatin analogue in clinical use, and pasireotide is a promising somatostatin analogue in development. Newer long-acting depot formulations are now available offering once-monthly administration. Although octreotide was initially developed for symptom control, recent results indicate that it also has an antiproliferative effect, significantly increasing time to progression in patients with midgut NETs. Combinations of octreotide with other targeted therapies may further improve patient outcomes. Findings in recent studies of the combination of octreotide and the mTOR inhibitor everolimus are encouraging. The combinations of octreotide with other agents (eg, interferon-α, bevacizumab, cetuximab, AMG-706, and sunitinib) are being investigated.

CONCLUSIONS: Somatostatin analogues have been used to treat the symptoms of NETs for decades and also have an antineoplastic effect, markedly prolonging progression-free survival. Somatostatin analogues are likely to remain the cornerstone of treatment for most patients with advanced NETs. Promising new combination therapies are undergoing clinical investigation.

Neuroendocrine tumors (NETs) are epithelial neoplasms that undergo predominantly neuroendocrine differentiation and arise in many organs of the body.[1] Although NETs are uncommon, the reported incidence has been steadily increasing. An analysis of 35,825 NET cases in the Surveillance, Epidemiology, and End Results database demonstrated a 5-fold increase in the annual age-adjusted incidence of NETs from 1.09/100,000 population in 1973 to 5.25/100,000 population in 2004.[2]

NETs are often classified by their organ of origin (eg, lung, pancreas, or gastrointestinal tract) and by their secretion of various peptides and neuroamines.[3] Functional NETs are defined by the presence of a clinical syndrome caused by excessive hormone secretion. An example is carcinoid syndrome from the secretion of serotonin and other vasoactive substances, resulting in diarrhea and flushing.[4] In contrast, nonfunctional NETs have no specific clinical syndrome but may still secrete peptides or neuroamines, measurable in plasma or urine. NETs are classified as either well differentiated (low and intermediate grade) or poorly differentiated (high grade). NET survival rates vary by primary site and grade and are lower in patients with poorly differentiated tumors than in those with

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well-differentiated tumors and in distant vs. locoregional disease.[2] This review is focused on the treatment of patients with well-differentiated NETs.

If NETs are diagnosed early, surgical resection is often curative.[5–7] However, the variable and nonspecific symptoms of NETs often delay diagnosis until the disease has progressed to an advanced state, when complete surgical resection may no longer be possible. More than 50% of NETs are unresectable at diagnosis.[8] Metastatic NETs can be treated with localized therapy for liver metastases (eg, resection, radiofrequency ablation, hepatic artery radioembolization, chemoembolization, and bland embolization) and systemic management with chemotherapy and biologic therapies (eg, interferon [IFN]-α, antiangiogenic drugs, mammalian target of rapamycin [mTOR] inhibitors, multikinase inhibitors, and peptide receptor radiotherapy).[4,9–11] Somatostatin analogues (SSAs) play a central role in managing the symptoms of excessive hormone secretion and appear to control tumor growth.[12–15]

SOMATOSTATIN AND ITS ANALOGS

Somatostatin

Somatostatin is a peptide hormone that mediates its inhibitory effects through binding to specific cell surface, G-protein–coupled receptors, of which five distinct subtypes (sst_1–sst_5) have been characterized.[16–18] Cells and tissues targeted by somatostatin frequently express multiple receptor subtypes, and tumors arising from these tissues generally express a high density of receptors.[19] In NETs, sst_2 expression predominates, although multiple other subtypes have also been found.[19] Well-differentiated tumors express somatostatin receptors more often, and at higher density, than do poorly differentiated tumors.[20] The activated somatostatin receptors mediate their inhibitory effects through at least 4 intracellular pathways. These include inhibition of adenyl cyclase, activation of K^+/Ca^{2+} channels, activation of protein phosphatases, and activation of intracellular tyrosine phosphatase.[20]

Somatostatin was initially viewed as a candidate for cancer treatment because of its ability to impede hormone release and cell growth after binding to its receptors.[21] Unfortunately, the short half-life of native somatostatin and the impact of rebound hypersecretion on discontinuation limit its use as a therapeutic agent. This prompted the development of clinically useful analogues with longer biological half-lives.[18,20,22]

Analogs of Somatostatin

In the 1980s, production of the 8-residue SSA octreotide (Sandostatin®; Novartis) was reported.[23] Several cyclic octapeptides soon followed, all of which demonstrated increased resistance to peptidase inactivation, substantially longer half-lives, and improved pharmacologic efficacy.[20] Unlike natural somatostatin, octreotide binds with high affinity only to the sst_2 receptor subtype and with lower affinity to the sst_5 receptor (Table 1). Octreotide does not cause rebound hormone hypersecretion.[19,24] The U.S. Food and Drug Administration (FDA) has approved octreotide for treating patients with several types of NETs. It is indicated for the severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and the profuse watery diarrhea associated with vasoactive intestinal polypeptide (VIP)-secreting tumors.[25] Another SSA in clinical use, lanreotide (Somatuline®; Ipsen), has a similar activity and affinity profile, although it has not yet been approved by the FDA for the treatment of patients with NETs. Pasireotide (SOM230; Novartis) is a cyclohexapeptide in clinical development.[19] Pasireotide has a more universal binding profile and mimics the action of natural somatostatin,[26] with high binding affinity for $sst_{1–3}$ and particularly high affinity for sst_5. Long-acting depot SSA formulations have also been developed. Octreotide long-acting repeatable (LAR) is administered intramuscularly once every 4 weeks.[27,28] Lanreotide prolonged-release (PR) is injected once every 10 to 14 days.[29,30] Lanreotide autogel (AG), administered by deep subcutaneous injection once every 4 weeks, is also available.[31] Pasireotide long-acting release, administered by intramuscular injection every 4 weeks, is being evaluated in clinical trials.

SSA: SAFETY PROFILE

Adverse Events

The most common adverse events related to octreotide treatment in patients with carcinoid or VIP-secreting tumors are nausea, abdominal pain, headache, dizziness, fatigue, and back pain[25,28] (Table 2). Local pain and erythema at the injection site

Table 1. Attributes of somatostatin and its analogs

Compound	Peptide size	Half-life (immediate-release products)	Binding affinity	Administration route	Development stage
Somatostatin	14/28 Amino acids	≤3 min	All receptors	IV	—
Octreotide	8 Amino acids	2 h	Primarily sst_2, plus sst_5	Octreotide acetate: IV, SC Octreotide LAR: IM	Approved and marketed
Lanreotide	8 Amino acids	2 h	Primarily sst_2, plus sst_5	Lanreotide: SC Lanreotide PR: IM Lanreotide AG: SC	Approved and marketed
Pasireotide	6 Amino acids	12 h	sst_5, plus $sst_{1–3}$	Pasireotide: SC Pasireotide LAR: IM	In clinical development

AG, autogel; IM, intramuscular; IV, intravenous; octreotide LAR, octreotide long-acting repeatable; pasireotide LAR, pasireotide long-acting release; PR, prolonged release; SC, subcutaneous.

Table 2. Overview of reported adverse events during octreotide LAR treatment[25,28]

Adverse event	Mean percentage of subjects with symptom
Most common with 10–30 mg/month octreotide LAR	
Nausea	31.3
Abdominal pain	22.4
Headache	20.9
Dizziness	19.4
Fatigue	16.4
Back pain	14.9
Biliary effects over 18 months of treatment	
Gallbladder abnormalities*	62
New gallstones	24
Glucose metabolism	
Hyperglycemia	27
Hypoglycemia	4
Cardiac events in patients with carcinoid syndrome	
Sinus bradycardia	19
Conduction abnormalities	9
Arrhythmias	3

*Includes jaundice, gallstones, sludge, and dilatation.
LAR, long-acting repeatable.

are also common, as is the case with other depot injections.[13] In a phase III study of patients randomly assigned to octreotide LAR (10–30 mg/month) or daily subcutaneous octreotide, 84% to 95.4% of patients reported adverse events, most of mild or moderate severity and thought to be unrelated to therapy.[28] A similar safety and tolerability profile was seen with octreotide, lanreotide, and pasireotide, all of which were generally well tolerated.[32,33]

Other studies have reported gastrointestinal toxicity, such as loose stool, mild steatorrhea, and flatulence. These adverse events may begin shortly after the first administration of drug and subside over subsequent weeks as treatment continues.[13] SSAs can cause steatorrhea by inhibiting the production of pancreatic digestive enzymes. Pancreatic enzyme supplementation is helpful in this context. Impaired glucose tolerance has also been observed during SSA therapy. The risk for gallstones or bile duct stones is increased with prolonged SSA treatment[13,25,28] (Table 2).

Drug Interactions

There are several known drug interactions with octreotide (and other SSAs), including interaction with cyclosporine, insulin, and bromocriptine (Table 3).[25,34] In most cases, drug monitoring and possible dose adjustment are all that is required.

SSA USE IN NETs

Overview of Clinical Experience

In a recent retrospective study of 146 patients with metastatic midgut NETs, of whom 91% had received long-term octreotide treatment, the overall 5-year survival rate was 75%, in contrast to a rate of just 19% in historical controls.[35] In phase II studies in patients with NETs receiving lanreotide PR 30 mg intramuscularly every 10 to 14 days, the rate of objective response was low (5%–8%), but a large percentage of patients (40%–49%) achieved stable disease; the median duration of disease stabilization was 8.5 to 9.5 months.[29,30] In a small-scale study of NET patients with hormone-related symptoms, treatment with lanreotide PR (30 mg every 14 days) was

shown to reduce or normalize the levels of tumor markers in 47% of the those assessed, whereas 87% had reduced or stabilized tumor size over the 6-month duration of the trial.[36] In a 9-year retrospective study involving 76 patients with metastatic midgut NETs and carcinoid syndrome, symptoms were well controlled with lanreotide AG alone in 74% of patients, with only 30% demonstrating radiologic progression.[37,38]

In a crossover study involving octreotide and lanreotide in patients with carcinoid syndrome, half the patients received octreotide 200 μg 2 or 3 times daily for 1 month, followed by lanreotide 30 mg intramuscularly every 10 days for 1 month, and the other half received the 2 drugs in the opposite order. Octreotide and lanreotide were equally effective in reducing symptoms of carcinoid syndrome and tumor biomarkers.[39] Direct comparison between most octreotide and lanreotide clinical studies cannot be made because of differences in study design (eg, inclusion criteria, tumor grade, extent of disease, and end points). However, in a review of almost 500 patients in 15 studies, it was noted that octreotide LAR achieved symptomatic relief in 74.2% of NET patients (range, 61.9%–92.8%), biochemical response in 51.4% (range, 31.5%–100%), and tumor response in 69.8% (range, 47.0%–87.5%).[20] Long-acting lanreotide resulted in similar levels of symptomatic relief (67.5%; range, 40.0%–100%), biochemical response (39.0%; range, 17.9%–58%), and tumor response (64.4%; range, 48.0%–87.0%).

Although SSA therapy effectively reduces symptoms of excessive hormone secretion in most patients, a considerable number experience escape from clinical response and return of symptoms.[37] In a phase II study, pasireotide 600 to 900 μg administered subcutaneously twice a day was evaluated in 45 patients with advanced NETs with symptoms of carcinoid syndrome inadequately controlled by octreotide LAR. Most (63.6%) had stage IV cancer at baseline. Pasireotide was effective at controlling diarrhea and flushing in 12 (27%) of the 44 patients included in the efficacy population.[37,40] Three of these patients achieved complete symptom control, and 9 experienced partial symptom control.

Table 3. Known or suspected drug interactions with octreotide LAR and resultant clinical requirements

Drug name	Effect of interaction with octreotide LAR	Clinical requirements
Cyclosporine[25]	Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.	Close monitoring of blood levels of cyclosporine and rejection antibodies in transplant recipients.
Insulin and oral hypoglycemic drugs[25]	Octreotide inhibits the secretion of insulin and glucagon.	Blood glucose level monitoring when initiating octreotide LAR treatment or when adjusting the dose and antidiabetic treatment alteration accordingly.
Bromocriptine[34]	Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine by 40% through the inhibition of CYP3A4 metabolism secondary to the suppression of growth hormones by octreotide.	Monitoring of patients for signs of ergotism and other dopaminergic symptoms.
Beta-blockers[25]	Concomitant administration of bradycardia-inducing drugs (eg, beta-blockers, calcium channel blockers, and other antiarrhythmics) may have an additive effect on the reduction of heart rate associated with octreotide.	Heart rate and blood pressure monitoring and dose adjustment of concomitant medication if necessary.
Compounds known to be metabolized by CYP enzymes[25]	Octreotide may decrease the metabolic clearance of compounds metabolized by CYP enzymes, possibly through the suppression of growth hormone.	Drugs mainly metabolized by CYP3A4 and with a low therapeutic index (eg, quinidine, terfenadine) used with caution.
Orally administered drugs[25]	Octreotide has been associated with alterations in nutrient absorption, thus resulting in possible absorption effects on orally administered drugs.	Monitoring and possible dosage adjustments of concomitant drugs.

CYP, cytochrome P450; LAR, long-acting repeatable.

In 23 patients evaluated for tumor response at study end, 13 had stable disease and 10 had progressive disease. It has been postulated that pasireotide, which has higher affinity for sst_1, sst_3, and sst_5 than octreotide and lanreotide, may offer symptom control in patients in whom disease is inadequately controlled with octreotide or lanreotide. Although this study did not meet the primary end point of achieving at least partial symptom control in 30% of the patients, the potential activity of pasireotide in patients with advanced NETs refractory to octreotide LAR warrants further investigation.

As mentioned earlier, octreotide has been approved by the FDA for the treatment of symptoms associated with carcinoid tumors. A distinct group of NETs is of pancreatic origin; many of these tumors are functional and produce hormone-related side effects. In a retrospective analysis of 191 duodenopancreatic NETs, there were 80 (42%) cases of insulinoma, 66 (35%) cases of gastrinoma, 12 (6%) cases of glucagonoma, and 6 (3%) cases of VIPoma.[41] In this patient context, octreotide is the only FDA-approved SSA, but is used solely for treating profuse, watery diarrhea in patients with VIPoma. However, the authors describe the routine clinical use of octreotide for the control of hormone-related symptoms in patients with these types of NETs. Octreotide is effective both before and after surgery and in patients with metastatic disease if surgery is not an option. A study evaluating lanreotide PR in patients with NETs and hormone-related symptoms included 6 patients with gastrinoma and 1 with VIPoma. Lanreotide PR 30 mg was administered by intramuscular injection every 14 days for 6 months. Four (67%) of the patients with gastrinoma and the patient with VIPoma showed symptomatic improvement (>50% reduction) and biochemical responses.[36] The use of SSAs in patients with functional pancreatic NETs deserves further clinical investigation.

In addition to reducing hormone production by NETs, SSAs have been reported to reduce upper abdominal pain, improve quality of life and performance status,[13] promote healing of pancreatic fistulae,[42] and improve orthostatic hypotension.[43]

Effect of SSAs on Tumor Growth

In addition to alleviating the symptoms of functional NETs, SSAs can inhibit the growth of NETs. Clinical trials have shown that SSAs can halt tumor progression, but patients rarely have objective tumor regression.[44] SSAs work both directly and indirectly to control tumor growth. The direct antimitotic effect is mediated by somatostatin receptors on tumor cells. Indirect effects of SSAs, such as inhibition of growth factor secretion, inhibition of angiogenesis, and immunomodulatory effects on peripheral target organs, also contribute to tumor control.[14,44] By suppressing the synthesis and secretion of growth factors, such as insulin-like growth factor (IGF)-1, an important modulator of many neoplasms, octreotide is able to exert antiproliferative effects and reduce tumor growth.[14] Angiogenesis can also be inhibited by SSAs. Compared with native somatostatin, octreotide and pasireotide are able to inhibit neovascularization to a greater extent, possibly through interactions with peritumoral vascular sst_2 receptors.[45,46] SSAs may also exert antiangiogenic effects through the inhibition of growth factors (eg, platelet-derived growth factor, IGF-1, and epidermal growth factor), which are known to stimulate important processes in angiogenesis, such as endothelial and smooth muscle cell proliferation.[47,48] Finally, because somatostatin receptors are expressed on various cells of the immune system (eg, lymphocytes,

monocytes), octreotide may regulate inflammatory and immune mechanisms, possibly enhancing its antiproliferative activity.[14]

Octreotide LAR in Midgut NETs: PROMID Study

PROMID was a prospective, randomized, placebo-controlled, double-blind, phase IIIb study in treatment-naive patients with locally inoperable or metastatic well-differentiated midgut NETs.[15] Eighty-five patients were randomly assigned to receive either octreotide LAR 30 mg/month intramuscularly or placebo for 18 months or until tumor progression or death.[15] The primary end point was median time to tumor progression. Octreotide LAR significantly increased the median time to tumor progression compared with placebo (14.3 months vs. 6.0 months, respectively; hazard ratio, 0.34; 95% confidence interval [CI], 0.20–0.59; P = .000072; Figure 1).[15] Prolongation of progression-free survival (PFS) by octreotide LAR was seen in patients with either functional or nonfunctional NETs. However, the effect of octreotide LAR on overall survival (OS) could not be established. The hazard ratio for OS was 0.81 (95% CI, 0.30–2.18; P = .77). Results from PROMID indicate that octreotide LAR significantly inhibits tumor growth in patients with metastatic midgut NETs.[15] In the United States, no somatostatin analogues or any other medications have been approved by the FDA for the management of asymptomatic carcinoid tumor. However, based on the results of the PROMID study, octreotide is frequently used as an antineoplastic to halt the growth of metastatic carcinoid and is, in fact, in the National Comprehensive Cancer Network (NCCN) treatment guidelines for this purpose.[6]

Lanreotide Autogel in Nonfunctioning Enteropancreatic Endocrine Tumors: CLARINET Study

The ongoing CLARINET study is a phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the effect of lanreotide autogel 120 mg administered by deep subcutaneous injection every 28 days on PFS in patients with nonfunctioning enteropancreatic endocrine tumors (ClinicalTrials.gov identifier, NCT00353496). The results of this study should determine whether lanreotide has an inhibitory effect on tumor growth in patients with advanced nonfunctioning neuroendocrine tumors of intestinal or pancreatic origin. Final data collection for the primary outcome measure is estimated to occur in June 2013.

PERIOPERATIVE USE OF SSAs

Octreotide use is critical in treating and preventing perioperative carcinoid crisis, a life-threatening condition in patients with metastatic functional NETs, usually triggered by anesthesia or surgical/radiologic procedures.[49] Carcinoid crisis is characterized by a sudden and profound decrease in or elevation of blood pressure, sometimes accompanied by tachycardia, elevated blood glucose, and severe bronchospasm. It can be fatal without pharmacologic intervention.[50] In a retrospective analysis of 119 patients who underwent abdominal surgery for metastatic functional NETs, none of the 45 who received intraoperative octreotide experienced carcinoid crisis, compared with 8 (11%) of the 73 who did not receive octreotide (P = .023).[49] The 2012 NCCN guidelines on NETs specifically state that octreotide therapy should be initiated in all patients before resection of primary or metastatic functional (carcinoid) endocrine tumors.[6]

In a pooled evaluation of data from 700 patients in 25 centers, octreotide LAR and lanreotide AG both controlled symptoms after surgical cytoreduction of metastases in up to 80% of patients, stabilized disease progression in approximately 50% to 80%, and reduced biomarkers in approximately 40%.[51] A second overview of NET management options in large, specialized referral centers also concluded that when residual tumor remained after surgery, long-acting SSAs were effective in managing symptoms.[52] Results of the PROMID study, in which octreotide LAR demonstrated antiproliferative activity in addition to symptom reduction, provide a further rationale for the use of long-acting SSA therapy in patients who have undergone cytoreduction.[15]

SSAs: DOSE OPTIMIZATION

The suggested daily dose of octreotide acetate for patients with carcinoid tumors during the first 2 weeks ranges from 100 to 600 μg/day in 2 to 4 divided doses, usually starting at the lower end of the range; the dose can be slowly escalated as tolerated. Dosage can be adjusted on an individual basis to control symptoms; some patients may require significantly higher doses (up to 1.5 mg/day).[25] After 2 weeks of daily injections, if not limited by toxicity, the first dose of octreotide LAR (20 mg by deep intramuscular injection) should be given. Doses of octreotide LAR (20 or 30 mg administered intramuscularly) are then repeated every 4 weeks.[25] To maintain steady
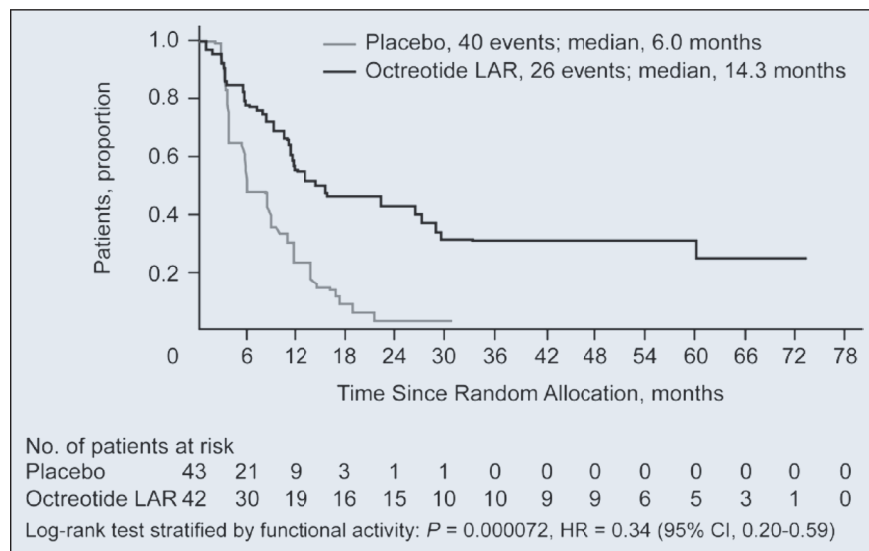
Figure 1. Conservative intent-to-treat analysis of time to progression or tumor-related death in PROMID.[15] Reprinted with permission. © 2009 American Society of Clinical Oncology. All rights reserved. Rinke A, et al. *J Clin Oncol* 27:4656–4663, 2009.

state blood levels and to reduce the risk for symptom exacerbation caused by a decrease in therapeutic blood level, it is recommended that subcutaneous octreotide be continued for 2 weeks after the first octreotide LAR injection. In patients who experience exacerbation of symptoms while receiving maintenance octreotide LAR, subcutaneous octreotide 300 μg administered 3 times/day as a "rescue" dose can be added. This commonly occurs in the days preceding a scheduled octreotide injection, when octreotide blood levels are at nadir. Monitoring of plasma octreotide levels may be helpful in treating patients with symptom exacerbation or cancer progression who are receiving conventional doses of octreotide, but its role in routine clinical practice is yet to be determined.[53]

In some patients with NETs, SSAs may lose effectiveness within months of treatment initiation, whereas in other patients, the NETs can be controlled for several years.[20] The reasons for tachyphylaxis are unclear but may be due to reduced somatostatin receptor concentration on NET cells. In some patients, increasing the dose may restore the original response.[53]

The highest approved dose of octreotide LAR is 30 mg administered intramuscularly every 4 weeks, though higher (eg, ≤60 mg every 4 weeks) or more frequent (30 mg every 14–21 days) doses have been used on occasion to control symptoms in patients refractory to conventional doses of octreotide.[54] Escalated doses of octreotide LAR (60 mg every 28 days) have proved both safe and effective in a subset of patients with active acromegaly inadequately controlled with long-term SSAs.[54] The results of one trial (ClinicalTrials.gov identifier, NCT00990535) evaluating more frequent doses (30 mg octreotide LAR every 21 days) in patients with NETs will be examined with interest (www.clinicaltrials.gov).

In a 6-month dose-titration study of 71 patients with carcinoid syndrome, the participants were administered 6 treatments of 28-day lanreotide PR by deep subcutaneous injection.[55] The first 2 were 90-mg doses, and subsequent doses were titrated (60, 90, 120 mg) based on symptom response. At 6 months, 11 (73%) of 15, 4 (33%) of 12, and 12 (27%) of 44 patients responded to lanreotide PR 60, 90, and 120 mg, respectively. A consequence of the dose-titration design of the study was that patients with severe symptoms were given higher doses. Therefore, nonresponders disproportionately received higher doses. Presumably, patients who responded to lower doses would also respond to higher doses. A more lucid statistic is that 27 (38%) of 71 patients responded to doses of lanreotide PR of 120 mg or less, 15 (21%) of 71 to 90 mg or less, and 11 (15%) of 71 to 60 mg. Dose optimization caused a reduction in episodes of flushing and diarrhea by a mean of 1.3 and 1.1 episodes/day, respectively (both $P \le .001$).

USE OF SSAs IN COMBINATION THERAPY

Octreotide LAR and other SSAs are likely to remain a cornerstone of therapy for NETs. However, several other therapeutic targets have emerged (Figure 2).[56] Recently, the mTOR inhibitor everolimus and the multi-targeted receptor tyrosine kinase inhibitor sunitinib were approved for the treatment of patients with advanced pancreatic NETs. However, the safety and efficacy of these agents have not been established for the treatment of nonpancreatic NETs. In recent years, the use of octreotide in combination with agents directed at other NET therapeutic targets, including mTOR, IGF-1 and its receptor, and various growth factors and cytotoxic agents (eg, vascular endothelial growth factor [VEGF] and IFN) have been investigated.[20,56]

mTOR, a critical regulator of cell growth, proliferation, metabolism, and angiogenesis, often has increased activity in NETs, stimulating research in mTOR inhibitors, such as everolimus, as therapeutic options.[56] Given that somatostatin receptors are known to modulate mTOR, a somatostatin analogue plus an mTOR inhibitor have been combined for potential synergy.[57,58] In a phase II study evaluating the impact of everolimus (5–10 mg/day) plus octreotide LAR (30 mg every 28 days) in patients with advanced low- to intermediate-grade NETs, 22% of patients had a partial response and 70% had stable disease.[59] The overall median PFS time was 60 weeks, and the 3-year survival rate was 78%.[59] The large, double-blind, placebo-controlled, phase III RADIANT-2 study demonstrated that octreotide LAR could be safely administered in combination with everolimus to patients with advanced NETs
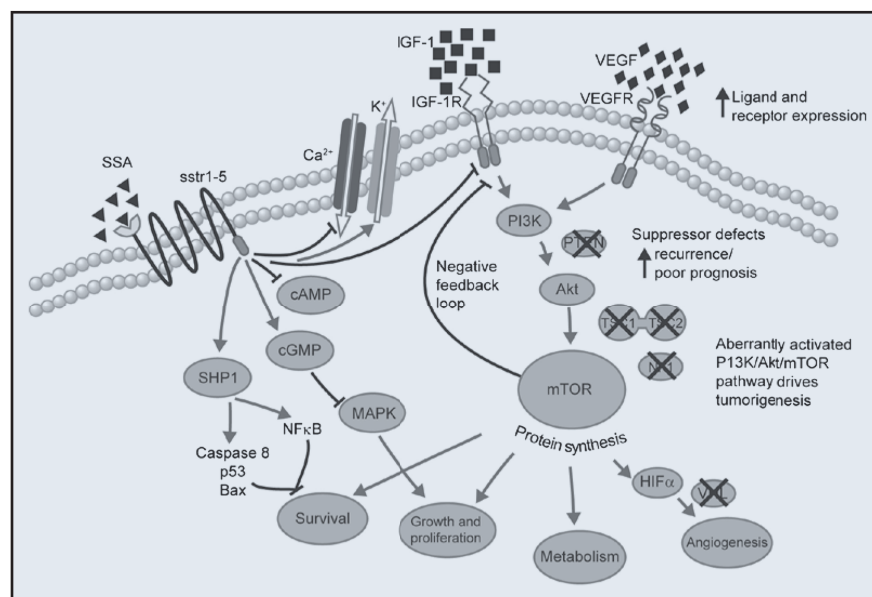
Figure 2. Select molecular mechanisms involved in NETs. cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; HIFα, hypoxia-inducible factor alpha; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NFκB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; SHP1, src homology region domain 2-containing phosphatase-1; SSA, somatostatin analog; sstr1–5, somatostatin receptor subtypes 1–5; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.[56] Reprinted with permission. © 2011 Adis Data Information BV. All rights reserved. Salazar R, et al. *Drugs* 71:841–852, 2011.

and a history of diarrhea, flushing, or both.[60]

The addition of an SSA to chemotherapy or biologic therapy may increase efficacy.[53] In a study of octreotide plus IFN-α vs. octreotide plus the antiangiogenic monoclonal antibody bevacizumab, the combination with bevacizumab appeared to improve objective response and PFS after 18 weeks of treatment (95% vs. 68% with IFN).[61] This combination is now being evaluated by a much larger clinical trial, SWOG 051, comparing octreotide plus IFN-α with octreotide plus bevacizumab. In a prospective, randomized, multicenter trial on the antiproliferative effects of lanreotide IFN-α, or the combination of the 2, in 80 patients with metastatic NETs, researchers found that lanreotide and IFN-α had comparable antiproliferative effects. However, the antiproliferative effects of the combination of lanreotide and IFN-α were not significantly better than those of either monotherapy. The combination of lanreotide and IFN-α did result in better symptom control, but side effects were more common.[62]

A phase I study of octreotide, everolimus, and the anti–IGF-1 receptor monoclonal antibody cetuximab in patients with low- to intermediate-grade NETs is recruiting participants (ClinicalTrials.gov identifier, NCT01204476). An ongoing phase II study (ClinicalTrials.gov identifier, NCT00427349) in patients with low-grade NETs is also evaluating the efficacy and safety of octreotide plus daily oral AMG-706, a multikinase inhibitor that selectively targets VEGF (www.clinicaltrials.gov). Tyrosine kinase inhibitors, such as sunitinib, may also have synergistic actions with SSAs in the management of NETs.[53]

CONCLUSIONS

SSAs represent the cornerstone of therapy for patients with advanced NETs. Octreotide, the first SSA to be developed, has more than 30 years of available clinical data, providing convincing demonstration of its efficacy and tolerability in thousands of patients. The SSA lanreotide has a similar activity and affinity profile in numerous clinical trials, although it has not yet been approved in the United States for the treatment of patients with NETs. The introduction of long-acting SSA formulations has further improved efficacy by providing a

sustained plasma level of active agent and increasing the period of symptom control from hours to as much as 4 weeks. Although SSAs were developed primarily to benefit patients with hormone secretion symptoms, recent data from the PROMID study indicate that octreotide also has an antiproliferative effect. The new multireceptor-targeted SSA pasireotide may be useful for patients in whom symptoms are no longer controlled by octreotide or lanreotide. The activity of an SSA may also be improved by combination with other antineoplastic therapies. Recent trials of octreotide LAR with the mTOR inhibitor everolimus are encouraging. Further studies are needed to assess other combinations with octreotide LAR and new SSAs to improve cancer control and symptom relief in patients with NETs.

REFERENCES

1. Klimstra DS, Modlin IR, Coppola D, et al: The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 39:707–712, 2010
2. Yao JC, Hassan M, Phan A, et al: One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26:3063–3072, 2008
3. Vinik AI, Woltering EA, Warner RR, et al: NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas* 39:713–734, 2010
4. Strosberg JR, Cheema A, Kvols LK: A review of systemic and liver-directed therapies for metastatic neuroendocrine tumors of the gastroenteropancreatic tract. *Cancer Control* 18:127–137, 2011
5. Kulke MH, Siu LL, Tepper JE, et al: Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting. *J Clin Oncol* 29:934–943, 2011
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Neuroendocrine Tumors. National Comprehensive Cancer Network Web site. Available at http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed May 22, 2012
7. Banfield A, Green S, Ramage JK: Neuroendocrine tumour management: a team approach. *Hosp Med* 66:37–42, 2005
8. Kim SJ, Kim JW, Han SW, et al: Biological characteristics and treatment outcomes of metastatic or recurrent neuroendocrine tumors: tumor grade and metastatic site are important for treatment strategy [abstract]. *BMC Cancer* 10:448, 2010
9. Shojamanesh H, Gibril F, Louie A, et al: Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma. *Cancer* 94:331–343, 2002

10. Kulke MH, Anthony LB, Bushnell DL, et al: NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 39:735–752, 2010
11. Raymond E, Dahan L, Raoul JL, et al: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 364:501–513, 2011
12. Aparicio T, Ducreux M, Baudin E, et al: Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *Eur J Cancer* 37:1014–1019, 2001
13. Oberg K, Kvols L, Caplin M, et al: Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 15:966–973, 2004
14. Susini C, Buscail L: Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol* 17:1733–1742, 2006
15. Rinke A, Muller HH, Schade-Brittinger C, et al: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 27:4656–4663, 2009
16. Patel YC, Srikant CB: Somatostatin receptors. *Trends Endocrinol Metab* 8:398–405, 1997
17. Nilsson O, Kolby L, Wangberg B, et al: Comparative studies on the expression of somatostatin receptor subtypes, outcome of octreotide scintigraphy and response to octreotide treatment in patients with carcinoid tumours. *Br J Cancer* 77:632–637, 1998
18. Strosberg JR, Nasir A, Hodul P, et al: Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. *Gastrointest Cancer Res* 2:113–125, 2008
19. De Herder WW, Hofland LJ, Van Der Lely AJ, et al: Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. *Endocr Relat Cancer* 10:451–458, 2003
20. Modlin IM, Pavel M, Kidd M, et al: Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther* 31:169–188, 2010
21. Harris AG: Future medical prospects for Sandostatin. *Metabolism* 39:180–185, 1990
22. Harris AG: Somatostatin and somatostatin analogues: pharmacokinetics and pharmacodynamic effects. *Gut* 35:S1–S4, 1994
23. Bauer W, Briner U, Doepfner W, et al: SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. *Life Sci* 31:1133–1140, 1982
24. Anthony L, Freda PU: From somatostatin to octreotide LAR: evolution of a somatostatin analogue. *Curr Med Res Opin* 25:2989–2999, 2009
25. Sandostatin LAR® depot (octreotide acetate for injectable suspension) [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Corporation, December 2011
26. Bruns C, Lewis I, Briner U, et al: SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. *Eur J Endocrinol* 146:707–716, 2002

27. Gillis JC, Noble S, Goa KL: Octreotide long-acting release (LAR): a review of its pharmacological properties and therapeutic use in the management of acromegaly. *Drugs* 53:681–699, 1997

28. Rubin J, Ajani J, Schirmer W, et al: Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol* 17:600–606, 1999

29. Ricci S, Antonuzzo A, Galli L, et al: Long-acting depot lanreotide in the treatment of patients with advanced neuroendocrine tumors. *Am J Clin Oncol* 23:412–415, 2000

30. Ducreux M, Ruszniewski P, Chayvialle JA, et al: The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. *Am J Gastroenterol* 95:3276–3281, 2000

31. Lightman S: Somatuline autogel: an extended release lanreotide formulation. *Hosp Med* 63:162–165, 2002

32. Ludlam WH, Anthony L: Safety review: dose optimization of somatostatin analogs in patients with acromegaly and neuroendocrine tumors. *Adv Ther* 28:825–841, 2001

33. Petersenn S, Schopohl J, Barkan A, et al: Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. *J Clin Endocrinol Metab* 95:2781–2789, 2010

34. Flogstad AK, Halse J, Grass P, et al: A comparison of octreotide, bromocriptine, or a combination of both drugs in acromegaly. *J Clin Endocrinol Metab* 79:461–465, 1994

35. Strosberg J, Gardner N, Kvols L: Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology* 89:471–476, 2009

36. Wymenga AN, Eriksson B, Salmela PI, et al: Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol* 17:1111, 1999

37. Kvols LK, Oberg KE, O'Dorisio TM, et al. Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide LAR: results from a phase II study. *Endocr Relat Cancer* 2012 Jul 17 [Epub ahead of print]

38. Khan MS, El-Khouly F, Davies P, et al: Long-term results of treatment of malignant carcinoid syndrome with prolonged release Lanreotide (Somatuline Autogel). *Aliment Pharmacol Ther* 34:235–242, 2011

39. O'Toole D, Ducreux M, Bommelaer G, et al: Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 88:770–776, 2000

40. Oberg KE: The management of neuroendocrine tumours: current and future medical therapy options. *Clin Oncol (R Coll Radiol)* 24:282–293, 2012

41. Proye CA, Lokey JS: Current concepts in functioning endocrine tumors of the pancreas. *World J Surg* 28:1231–1238, 2004

42. Phelan HA, Minei JP: Pancreatic trauma: diagnostic and therapeutic strategies. *Curr Treatment Options Gastroenterol* 8:355–363, 2005

43. Lamarre-Cliche M: Drug treatment of orthostatic hypotension because of autonomic failure or neurocardiogenic syncope. *Am J Cardiovasc Drugs* 2:23–35, 2002

44. Eriksson B, Oberg K: Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: future outlook. *Ann Oncol* 10(suppl 2):S31–S38, 1999

45. Barrie R, Woltering EA, Hajarizadeh H, et al: Inhibition of angiogenesis by somatostatin and somatostatin-like compounds is structurally dependent. *J Surg Res* 55:446–450, 1993

46. Kumar M, Liu ZR, Thapa L, et al: Antiangiogenic effect of somatostatin receptor subtype 2 on pancreatic cancer cell line: inhibition of vascular endothelial growth factor and matrix metalloproteinase-2 expression in vitro. *World J Gastroenterol* 10:393–399, 2004

47. Woltering EA, Watson JC, Perin-Lea RC, et al: Somatostatin analogs: angiogenesis inhibitors with novel mechanisms of action. *Invest New Drugs* 15:77–86, 1997

48. Hayry P, Raisanen A, Ustinov J, et al: Somatostatin analog lanreotide inhibits myocyte replication and several growth factors in allograft arteriosclerosis. *FASEB J* 7:1055–1060, 1993

49. Kinney MA, Warner ME, Nagorney DM, et al: Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth* 87:447–452, 2001

50. Kvols LK, Martin JK, Marsh HM, et al: Rapid reversal of carcinoid crisis with a somatostatin analogue. *N Engl J Med* 313:1229–1230, 1985

51. Modlin IM, Kidd M, Latich I, et al: Current status of gastrointestinal carcinoids. *Gastroenterology* 128:1717–1751, 2005

52. Van Der Lely AJ, De Herder WW: Carcinoid syndrome: diagnosis and medical management. *Arq Bras Endocrinol Metabol* 49:850–860, 2005

53. Vinik AI, Anthony L, Boudreaux JP, et al: Neuroendocrine tumors: a critical appraisal of management strategies. *Pancreas* 39:801–808, 2010

54. Giustina A, Bonadonna S, Bugari G, et al: High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial. *Eur J Endocrinol* 161:331–338, 2009

55. Ruszniewski P, Ish-Shalom S, Wymenga M, et al: Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 80:244–251, 2004

56. Salazar R, Reidy-Lagunes D, Yao J: Potential synergies for combined targeted therapy in the treatment of neuroendocrine cancer. *Drugs* 71:841–852, 2011

57. Grozinsky-Glasberg S, Franchi G, Teng M, et al: Octreotide and the mTOR inhibitor RAD001 (everolimus) block proliferation and interact with the Akt-mTOR-p70S6K pathway in a neuro-endocrine tumour cell line. *Neuroendocrinology* 87:168–181, 2008

58. Bousquet C, Lasfargues C, Chalabi M, et al: Current scientific rationale for the use of somatostatin analogs and mTOR inhibitors in neuroendocrine tumor therapy. *J Clin Endocrinol Metab* 97:727–737, 2012

59. Yao JC, Phan AT, Chang DZ, et al: Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 26:4311–4318, 2008

60. Pavel ME, Hainsworth JD, Baudin E, et al: Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT 2): a randomised, placebo-controlled, phase 3 study. *Lancet* 378:2005–2012, 2011

61. Yao JC, Phan A, Hoff PM, et al: Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol* 26:1316–1313, 2008

62. Faiss S, Pape UF, Böhmig M, et al: Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors: the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol* 21:2689–2696, 2003

Disclosures of Potential Conflicts of Interest